Section: Respiratory Medicine

Original Research Article

DIAGNOSIS AND TREATMENT OUTCOME OF TUBERCULOUS MENINGITIS IN TERTIARY CARE HOSPITAL – TAMIL NADU

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Abstract

Background: Tuberculous Meningitis (TBM) is the most lethal form of tuberculosis. Early diagnosis of TBM remains to be a great challenge for the physicians as the clinical features such as fever, headache, vomiting remains to be non specific. There are many challenges in the diagnosis and treatment of TBM. The aim of this study is to do situational analysis of diagnosis and treatment outcome of TBM in tertiary care hospital, Tamil Nadu. **Materials and Methods:** A total of 50 patients with Tuberculous Meningitis (TBM) were recruited from Tirunelveli Medical College Hospital between January 2020 and June 2021. **Result:** In our study among 50 patients, TBM was commonly involved among the age group of 11-30 years, which represents about 38% of the patients. Males were more commonly affected compare to the females. Most common presenting symptom was fever (94%) and headache (80%). Most of them presented under the Medical Research Council (MRC) clinical stage 2 and 3 (84%) with the CSF profile analysis showing protein and lymphocytes count moderately elevated in 2/3rd of patients, and low glucose level in seventy percentage of patients and Globulin positive in 70% of the patients. Among 50 patients two patients had been diagnosed microbiologically with positive CBNAAT test. Meningeal enhancement and hydrocephalus was the most common neuroimaging findings. About ten percentage of patients were associated with pulmonary Tuberculosis. All patients were treated with standardized FDC regimens and selected patients treated with corticosteroids initial period and most of the patients received ATT for 9 months (83%) in our study. Microbiologically diagnosed patients had completed the treatment without any neurological sequel. Among clinically and radiologically diagnosed patients, 70% completed treatment and 18% reported to have persistent neurological deficit. **Conclusion:** Our findings underscore the complexity of TBM management, emphasizing the need for improved diagnostic tools and targeted therapeutic interventions to enhance treatment outcomes and minimize neurological sequelae in affected individuals. Further research is warranted to explore innovative approaches in tackling the challenges associated with the diagnosis and treatment of Tuberculous Meningitis.

INTRODUCTION

Tuberculosis is a chronic granulomatous infectious disease which is caused by mycobacterium tuberculosis bacilli producing a major global health problem worldwide.[1] It is transmitted by respiratory droplets expelled during coughing, also through infected milk. It affects the pulmonary and extrapulmonary organs.[2] The annual incidence of TB is about 13 million populations around the world among them 5% - 15% develop neurological TB and 70%-80% contributes Tuberculous Meningitis (TBM).[2-4] TBM is the most lethal form of tuberculosis, which when treated has a mortality of approximately 25% among HIV negative patients and can exceed more than 60% among the HIV positive patients.[1,3] Majority of TBM patient will present with neurological sequelae. Early diagnosis of TBM remains to be a great challenge for the physicians as the clinical features such as fever, headache, vomiting remains to be nonspecific.[4]

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There are many challenges in the diagnosis and treatment of TBM. It is mainly because of the paucity of bacilli in TBM when compared to pulmonary tuberculosis. The isolation of the organism from culture is the gold standard diagnostic method in which there is decreased sensitivity around 25% to 70%.[5] Therefore the physicians cannot always rely on culture for detecting drug sensitivity for initiating treatment. Nowadays for detecting drug sensitivity we have come up with CBNAAT and line probe assay technique reporting within hours to days.[4,5] The treatment of TBM is same as the treatment of pulmonary tuberculosis with increase in duration of the course extending from 9 to 12 months. There are limited guidelines for the treatment of patients with TBM. Hence, the efficacy of Anti Tuberculous therapy in TBM is unclear. Our study aims to determine the situational analysis of diagnosis and factors influencing the treatment outcome of TBM in tertiary care hospital, Tamil Nadu.

MATERIALS AND METHODS

A total number of 50 patients who visited the Tirunelveli Medical College hospital in the period of January 2020 and June 2021 with TBM were included. A structured proforma was obtained containing basic characteristics of patients that includes age, sex, occupation, place, presenting complaints, MRC staging, investigations (CSF analysis and radiological investigations) done and treatment given. Basic laboratory investigations like complete blood count, liver function test, renal function test, random blood glucose level, HIV test was done. Chest radiography and Sputum AFB test were done to rule out pulmonary tuberculosis.

Patients selected were diagnosed based on clinical history and examination, CSF findings, radiological findings and microbiological isolation of MTB. Many patients were diagnosed as TBM analysing clinical history, CSF analysis and radiological findings rather than the microbiological MTB identification or isolation. CSF analysis indicative of TBM include protein levels and lymphocyte count elevated, glucose level < the plasma glucose level. Radiologically - meningeal enhancement, basal exudates, tuberculoma were the most common findings.

MRC clinical staging of illness: In the context of assessing neurological conditions, three distinct stages can be identified. In Stage 1, individuals are fully conscious and exhibit no signs of paresis. However, as we progress to Stage 2, there is a noticeable decrease in the level of consciousness, but no significant neurological deficits are present. Finally, in Stage 3, patients are deeply comatose, and this stage may be accompanied by focal neurological deficits.

Definitions of Outcome: Treatment Completed: Defined as a TB patient who completedtreatment without clinical evidence of failure but with no record to showcomplete resolution by radiological or bacteriological evidence ofpersisting infection by the last month of treatment, either because testwere not done or because are unavailable.

Lost to Follow Up: A TB patients who did not start treatment orwas interrupted for 2 or more consecutive months.

Treatment Failure: A patient who has no satisfactory clinical orimaging response to treatment after completing 3-6 months ATT.

Died: A TB patient who dies for any reason before starting or during thecourse of treatment.

RESULTS

Number of patients in this study were 50, after achieving the necessary inclusion criteria, the following results were obtained. Characteristics of study subjects were shown in [Table 1]. Majority of the patients belong to the age group of 11-30 years (38%). Over all TBM had male preponderance with ratio of 1.17:1 as analysis from this study. Of the diverse manifestations of TBM, the common symptoms in the patients with TBM presenting in our study was head ache and fever which are the important symptoms for diagnosis of TBM according to Ahuja et al criteria. The common signs presented are altered sensorium, seizures, focal neurological deficits in the form of hemiparesis or hemiplegia, Para paresis and cranial nerve palsy. Most common MRC staging presented in our study belongs to stage 2.

The CSF examination findings in 50 patients with MRC staging of TBM were shown in [Table 2]. About 50 patients we were able to demonstrated the organism in the CSF CBNAAT only in two patients. Among patients diagnosed with TBM, specific radiological findings can shed light on the characteristic patterns observed during imaging studies. Meningeal enhancement, occurring in 56% of cases, is a prevalent feature, indicative of inflammation in the meninges. Hydrocephalus, noted in 16% of instances, highlights the buildup of cerebrospinal fluid within the brain. Basal exudates, affecting 10% of patients, are a sign of inflammatory exudative material at the base of the brain. Granulomas, observed in 6% of cases, signify the formation of nodular, inflammatory tissue. Remarkably, 12% of TBM cases appear entirely normal on radiological examinations, underscoring the importance of a comprehensive clinical assessment to complement imaging findings in diagnosing and managing this complex neurological condition.

Treatment outcome: Outcome of Anti Tuberculous Therapy in TBM, among 50 patients, 8 patients died during the course of treatment due toseverity of the disease. Out of the remaining 42 patients, 6 patients lost tofollow up. So 36 patients with TBM were followed up fortreatment outcome

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Among the 50 patients most common complication was epilepsy 10% followed by Focal neurological deficit 6% and Hydrocephalus 2%.

Table 1: Characteristics of study subjects

Characteristics	Number (n)	Percentage (%)
Age group (years)		
0-10	4	8
11-30	19	38
31-50	16	32
≥ 51	12	24
Gender		
Male	27	54
Female	23	46
Clinical Features		
Headache	40	80
Fever	47	94
Altered sensorium	36	72
Meningeal signs	33	66
Focal Deficit	13	26
Seizures	11	22
Vision impairment	5	10
Radiological Findings		
Meningeal Enhancement	28	56
Basal Exudate	5	10
Granuloma	3	6
Hydrocephalus	8	16
Normal	6	12
Treatment Outcome		
Treatment Completed	36	72
Lost to follow -up	6	12
Died	8	16
Treatment Failure	Nil	Nil

Table 2: Cerebrospinal fluid analysis findings with MRC clinical staging of TBM

Variables	Stage 1 (n=8)	Stage 2 (n=30)	Stage 3 (n=12)	Percentage (%)
1.Protein mg/dl				
<100	4	6	3	26
101-500	4	24	9	74
2.Cells				
<20 lymphocyte	4	3	8	30
>20 lymphocyt	4	22	9	70
3.Sugar				
Normal	6	15	4	50
<2/3rd S.levels	2	15	8	50
4.Globulin positive	5	20	12	74
5.AFB/CBNAAT	0	1	1	4
6.ADA	0	2	3	10

Table 3: Correlation of treatment outcome with MRC clinical staging of TBM

Variable	Stage 1	Stage 2	Stage 3	P value
Treatment Completed (36)	8	23	5	0.003
Died (8)	0	2	6	
Lost to follow-up (6)	0	5	1	

DISCUSSION

Among the 50 patients with TBM in our study majority of patients affected belongs to the age group of 11-30 years, approximating about 38% of the patients in the study. Next group of patients belongs to the age group of 31-50 years approximates to 32% of patients in the study. The study results were compared to Bella Devaleenal Daniel et al which interpreted with peak incidence belonging to 11-30 years.[6-16]

The gender preponderance in our study had a male preponderance of 54% and female 46%, which was compared to Mihaja raberahona et al results which showed that 56% of male and 44% of female were affected with TBM.[7] Bell Devaleenal Daniel et al also showed males were more affected than female.[6] The most common presentation of TBM in our study was fever (94%) and headache (80%), which was similar to Jann tay wang et al where 90% presented with fever and 76% had headache.[8] Mihaja raberahona et al showed nearly same as our study result with 96% had fever and 77% had headache.[7] Bella et al studied clinical presentation in TBM where children were commonly presented with headache and fever.[6]

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In our study of TBM majority of the patients falls under stage 2 (60%) and stage 3 (24%) according to MRC clinical staging system of the illness, which was indistinguishable with the Wang et al result where 52% were in stage 2 and 26.4% in stage 3.[8] Comparing with Mihaja raberahona et al result its almost same number of patients presented with advanced clinical stage 82% (stage 2 and stage 3).[7] Thilothammal et al study analysis interpreted that MRC stage 2 and stage 3 was the common clinicalstage of presentation. They analysed that the age of presentation and the MRC clinical stage of the illness were the prognostic factors which decided the outcome TBM.

In our study, CSF analysis was done in the patients with TBM at the time of diagnosis showed elevated protein level. The CSF protein level had mild elevation in 26% of the patients (<100 mg/dl), and 74% had moderate elevation (101 – 500 mg/dl). These values were correlated with clinical severity of illness. Sixty percentage of patients presented with stage 2 and stage 3 illness had moderate elevation of CSF protein level. Thilothommal et al analysed that 56% of the children with TBM had elevated protein especially with stage 2 and stage 3.[9] Yaramis et al reported that around 80% of CSF parameters from children affected with TBM had elevation of protein and lymphocytes.[10]

CSF glucose level were normal in 50% of the patients and reduced less than 2/3rd of plasma level in 50% of patients, which was indistinguishable with Mihaja et al result which reported about 45% had low CSF glucose.[7] In our study 70% of the patients revealed tuberculous range of lymphocytic pleocytosis that is >20%. Solomans et al observed >50% CSF lymphocytes in 89% of patients involved his study.[11]

In our study, we isolated the acid fast bacilli from the cerebrospinal fluid in only two cases (4%) by CBNAAT technique. The Gold standard method for the diagnosis of TBM was the detection of the M. tubercle bacilli in the CSF, either by smear examination or by bacterial culture. Currently the molecular diagnostic method was widely used for the rapid detection of MTB and its drug resistance. A minimum quantity of CSF sample to be collected is 5 ml [Preferably 10-15 ml]. Bella et al showed CSF sensitivity about 20% in AFB/Culture and CBNAAT test.[6]

Our study revealed that the most common finding on Radiological imaging in patients with TBM was meningeal enhancement [56%], followed by hydrocephalus [16%], basal exudates [10%] and granulomas [6%]. Meningeal enhancement and hydrocephalus was the commonest finding. Bella et al reported that Hydrocephalus was most common findings in neuroimaging which was incongruent with our study results.[6] Goyal et al study reported that Meningeal enhancement was seen in approximately 60% of patients with tuberculous meningitis.[12]

In our study following complications were observed a seizure (10%) followed by focal neurological deficit (6%) and hydrocephalus (2%). Compared to Mihaja et al study which reported cranial nerve palsy in 17% of patients, and focal neurological deficit (10%).[7] Van well et al reported 16% of children had normal, 52% had mild sequel and 19% had severe sequel.[13] Wang et al revealed most common complication was hydrocephalus followed by focal deficit, which showed disparity with our study result.[8] TBM associated with pulmonary tuberculosis was reported to be 10% which includes 6% of pulmonary TB and 4% of military TB. This was compared to Mihaja et al study which showed 6.7% pulmonary TB that was close to our study.[7]

In our study the outcome of management with the standard FDC regimen showed a success rate (treatment completed) of (72%), lost to follow up in12%, and death was recorded in 16% of patients. Compared to the studies from Kerala (n=32) done by Venugopal et al who registered 32 cases of TBM under Standard ATT regimen 29 patients among them completed treatment and were asymptomatic at the end of treatment (85%). All patients in their study were treated with intermittent regimen for 9 months as per RNTCP guidelines. Five patients (14%) died during treatment.[14] This study results were close to our study result.

Our study revealed that most of the death had occurred in patients under MRC stage 2 and 3, which was congruent with Bella et al study results (6). Lanwen et al revealed that death was 22% and most of them died in stage 2 and 3 clinical illness, which was close to our study result. Wang et al study reported death in 27% who underwent treatment duration of 6 months and 22% in 9 months duration of treatment.[8] Comparing to our study 16% of death was reported in patients who had undergone treatment less than 6 months of duration. Miftode et al reported that children had highest neurological deficit however mortality rate was similar to adult.[15] Shaw et al showed that elderly patients had higher risk of death when compare to younger patients.[16]

In our study the microbiologically diagnosed patients completed the treatment without persistent neurological sequel. Clinically and radiologically diagnosed patients where 70% completed the treatment and among them 18% had persistent neurological sequel.

American Thoracic Society recommended standard ATT regimens for duration of 9 – 12 months.[17]73 In our study standard fixed dose combination regimen was followed for a duration of 6 months by 8.3% patients, for 9 months by 83% of the patients and 12 months by 8.3% of patients. Early diagnosis of TBM was the most paramount partas the early initiation of antituberculosis treatment in these patient shows a favorable outcome without neurological sequel.

CONCLUSION

TBM is a disease that predominantly affects a younger demographic, with a notable prevalence

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among individuals aged 11 to 30 years, and it displays a male preponderance. The most common initial symptoms include fever and headaches, which serve as important clinical markers. Strikingly, patients often present with advanced MRC staging, typically falling into stage 2 and stage 3 of the disease, underlining the severity of their condition. The most frequent complication of this ailment is the occurrence of seizures, followed closely by the development of focal neurological deficits, highlighting the urgent need for timely intervention and treatment. Radiological imaging in TBM commonly reveals meningeal enhancement and hydrocephalus as the predominant findings, significantly aiding in the diagnostic process. Approximately 10% of TBM cases exhibit concomitant pulmonary Tuberculosis, emphasizing the systemic nature of this infectious disease. The treatment outcomes with the standard Fixed-Dose Combination (FDC) regimen indicate a 72% success rate, a 12% rate of patients lost to follow-up, and a 16% mortality rate, emphasizing the importance of effective management and adherence. Notably, patients with microbiologically diagnosed TBM tend to experience better treatment outcomes with a reduced risk of neurological sequelae. A treatment regimen spanning around 9 months results in more favorable outcomes in managing TBM, underscoring the necessity of completing the full course of antituberculosis treatment. Early diagnosis proves crucial, as the timely initiation of antituberculosis treatment regimens stands out as the most pivotal factor in determining the overall outcome and prognosis for these patients.

Limitations

This study had notable limitations. Firstly, it featured a smaller sample size, potentially affecting the generalizability of the findings. Furthermore, it was conducted at a single center, which might limit the diversity and broader applicability of the results. Another critical limitation was that the diagnosis of TBM in many patients relied on clinical and radiological imaging, which exhibited lower specificity when compared to cases microbiologically diagnosed. This variation in diagnostic methods could introduce biases and impact the accuracy of the results. Additionally, determining drug-resistant patterns proved challenging due to the variable sensitivity of microbiological investigations conducted on cerebrospinal fluid (CSF), and drug susceptibility tests were not administered to all patients, further complicating the comprehensive understanding of drug resistance in this context.

REFERENCES

1. Sharma SK, Mohan A. Extrapulmonary tuberculosis. IndianJ Med Res 2004;120:316-53.
2. LS Farer, LM Lowell, MP Meador. Extrapulmonary tuberculosis in the United States. Am J Epidemiology 1979;109: 205–17.
3. Tandon PN, Bhatia R, Bhargava S. Tuberculous meningitis.In: Harris AA, editor. Handbook of clinical neurology[revised series]. Amsterdam: Elsevier Science; 1988.p.195-226.
4. TUBERCULOSIS SHARMA editors surrender k.sharma third edition page no 230-249)
5. Kumar D, Watson JM, Charlett A, Nicholas S, DarbyshireJH. Tuberculosis in England and Wales in 1993: results of anational survey. Public Health Laboratory Service/BritishThoracic Society/Department of Health Collaborative Group.Thorax 1997;52:1060-7.
6. Daniel BD, Grace GA, Natrajan M. Tuberculous meningitis in children: Clinical management & outcome. Indian J Med Res. 2019 Aug;150(2):117-130.
7. Raberahona M, Rakotoarivelo RA, Razafinambinintsoa T, Andrianasolo RL, Randria MJ. Clinical Features and Outcome in Adult Cases of Tuberculous Meningitis in Tertiary Care Hospital in Antananarivo, Madagascar. Biomed Res Int. 2017;2017:9316589.
8. Wang JT, Hung CC, Sheng WH, Wang JY, Chang SC, Luh KT. Prognosis of tuberculous meningitis in adults in the era of modern antituberculous chemotherapy. J Microbiol Immunol Infect. 2002 Dec;35(4):215-22.
9. Thilothammal N, Krishnamurthy PV, Banu K, Ratnam SR. Tuberculous meningitis in children – Clinical profile, mortality and morbidity of bacteriologically confirmed cases. Indian Pediatr 1995; 32 : 641-7.
10. Yaramiş A, Gurkan F, Elevli M, Söker M, Haspolat K, Kirbaş G, et al. Central nervous system tuberculosis in children: A review of 214 cases. Pediatrics 1998; 102 : E49.
11. Solomons RS, Visser DH, Friedrich SO, Diacon AH, Hoek KG, Marais BJ, et al. Improved diagnosis of childhood tuberculous meningitis using more than one nucleic acid amplification test. Int J Tuberc Lung Dis 2015; 19 : 74-80.
12. Goyal V, Elavarasi A, Abhishek, Shukla G, Behari M. Practice Trends in Treating Central Nervous System Tuberculosis and Outcomes at a Tertiary Care Hospital: A Cohort Study of 244 Cases. Ann Indian Acad Neurol. 2019 Jan-Mar;22(1):37-46.
13. van Well Gijs T J, Paes Berbe F, Schoeman Johan F, et al. Twenty Years of Pediatric Tuberculous Meningitis: A Retrospective Cohort Study in the Western Cape of South Africa. Pediatrics. 2009;123:e1–e8.
14. Venugopal K, Sreelatha PR, Philip S, Kumar V. Treatment outcome of neuro tuberculosis patients put on DOTS--an observation study from the field. Indian J Tuberc. 2008 Oct;55(4):199-202.
15. Miftode E. G., Dorneanu O. S., Leca D. A., et al. Tuberculous meningitis in children and adults: a 10-year retrospective comparative analysis. PLoS ONE. 2015;10(7).
16. Shaw J. E. T., Pasipanodya J. G., Gumbo T. Meningeal tuberculosis: high long-term mortality despite standard therapy. Medicine. 2010;89(3):189–195.
17. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep. 2003 Jun 20;52(RR-11):1-77. Erratum in: MMWR Recomm Rep. 2005 Jan 7;53(51):1203.

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